Remarks and Arguments

Reconsideration of the above-identified application, in view of the following remarks, is respectfully requested.

I Status Of The Claims

Claims 1-10 and 12-14 are pending before entry of this amendment.

Claims 8 and 9 have been canceled without prejudice. Claims 1 and 14 have been amended to delete the phrases "or preventing," "or prevent" and "or at risk thereof." New claims 19-21 have been added. Support for the new claims may be found, for example, in the specification, at page 11, line 20, page 12, lines 19 and 25, page 13, lines 3 and 8, and page 14, line 28 to page 15, line 5.

Claims 1-7, 10, 12-14 and 19-21 are pending in this application and are at issue.

II Objection to the Abstract of the Disclosure

The Abstract has been objected to because it contains over 150 words. An amended Abstract is presented herein at page 2 that renders this objection moot. Entry of the amended Abstract and withdrawal of the objection is respectfully requested.

III The Rejections under 35 U.S.C. § 112, "Written Description"

Claims 1-3, 7-10 and 12-14 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. The Examiner asserts that there is inadequate written description for the terms "dual norepinephrine serotonin reuptake inhibitor(s)" "triple reuptake inhibitors" and "aminocyclopropane derivatives" and that there is no means for the skilled artisan to determine exactly what these compounds are aside from the explicitly named compounds at pages 10-13 of the specification (emphasis in Office Action at page 4).

Claim 14 has been amended to recite the compounds explicitly named at pages 10-13 of the specification (namely milnacipran, bicifadine, sibutramine, venlafaxine,

duloxetine, and pharmaceutically acceptable salts thereof). Accordingly, the rejection of claim 14 has been overcome and should be withdrawn.

Applicants also note that claims 4-6, which recite the specific NSRI milnacipran, were not rejected under for lack of written description. Furthermore, new claims 19-21 do not recite any of "dual norepinephrine serotonin reuptake inhibitor(s)" "triple reuptake inhibitors" or "aminocyclopropane derivatives". Accordingly, these new claims do not lack written description.

The rejection of claims 1-3, 7-10 and 12-14 is not believed to be well taken and is respectfully traversed.

The Examiner asserts that there is no written description with respect to the structural features that characterize these genera of compounds, such as "aminocyclopropane derivatives" recited in claim 10, and that no guidance as to how to make the compounds has been provided. Furthermore, the Examiner asserts that essential material (describing, for example, methods of synthesizing compounds) has been improperly incorporated into the specification. See page 4 of the Office Action.

Applicants respectfully disagree with the Examiner. The name "aminocyclopropane" derivatives clearly suggests to one of ordinary skill in the art what structural features are present, namely a cyclopropane group and an amino substituent. Moreover, suitable aminocyclopropane derivatives, and syntheses thereof, are described in U.S. Patent Nos. 5,621,142 and 4,478,836, which are disclosed in Applicant's specification at page 11, lines 17 and 23, and incorporated by reference at page 21, lines 29-31. An application for a patent when filed may incorporate "essential material" by reference to (1) a U.S. patent, (2) a U.S. patent application publication, or (3) a pending U.S. application. See M.P.E.P. § 608.01(p). Accordingly, one of ordinary skill in the art, with reference to the specification, would clearly appreciate suitable aminocyclopropane derivatives that could be used in the present invention, and would readily be able to synthesize such compounds.

Claims 8 and 9 have been canceled, rendering the rejection of these claims moot.

In view of the above amendments and arguments, withdrawal of the rejection is respectfully requested.

IV The Rejections under 35 U.S.C. § 112, "Enablement"

Claims 1-10 and 12-14 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner concedes, at page 5 of the Office Action, that the specification is enabling for treating DSP, but asserts that no enablement is provided for the total prevention of DSP.

While Applicants respectfully disagree with the Examiner, in order to further prosecution of this application, claims 1 and 14 have been amended to delete the phrases "or preventing," "or prevent" and "or at risk thereof."

Accordingly the rejection is now moot and should be withdrawn.

V. Rejections under 35 U.S.C. § 103

Claims 1-7 and 12-13 stand rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 4,478,836 to Mouzin *et al.* ("Mouzin") in view of Moret *et al.*, *Neuropharmacology*, 24:12, 1211-19 (1985) ("Moret") and Ruoff, *J. Family Practice*, 43:6, S25-S34 (1996) ("Ruoff").

Applicants note that claim 10 (directed to a method of treating DSP by administering at least two of milnacipran, sibutramine, and an aminocyclopropane derivative) and claim 14 (directed to a method of treating DSP, wherein the DSP comprises atypical depression characterized by mood reactivity and neurovegetative symptoms present for more than about two weeks) are not rejected 35 U.S.C. § 103(a) as obvious over the cited references. Moreover, new claim 19 is dependent from claim 14, and is therefore also not obvious over the cited references.

Applicants submit that new claim 20 (directed to a method of treating DSP by administering milnacipran and or more active compounds selected from antidepressants, analgesics, muscle relaxants, anorectics, stimulants, antiepileptic drugs, sedatives, hypnotics, and combinations thereof) and new claim 21, dependent therefrom, are also

not obvious over the cited references for the same reasons that claim 10 is not obvious. Mouzin, Moret and Ruoff, alone or in combination, do not teach or suggest a method of treating DSP by administering a combination of milnacipran and one or more antidepressants, analgesics, muscle relaxants, anorectics, stimulants, antiepileptic drugs, sedatives or hypnotics.

The rejection of claims 1-7 and 12-13 is not believed to be well taken and is respectfully traversed.

The Examiner continues to assert that the prior art provides ample motivation to combine Mouzin and Moret with Ruoff, asserting that the fact that Ruoff teaches that venlafaxine is associated with side effects does not teach away from the claimed methods, as venlafaxine is only one example of an NSRI that happens to be associated with side effects.

Contrary to the Examiner's assertions, the disclosure of Ruoff would clearly lead a person of ordinary skill in the art away from using a norepinephrine serotonin reuptake inhibitor (NSRI) or triple reuptake inhibitor (TRI), as recited in the present invention.

The only NSRI disclosed in Ruoff is venlafaxine, which is disclosed to be associated with serious side-effects including nausea, vomiting, blood pressure, increase, sexual dysfunction, sweating and somnolence. *See* Ruoff page S30. Indeed, Ruoff states, for example at page S28, that therapy should be tailored to individual patients based on several factors, one of which is the side-effect profile. In fact, Ruoff discloses that, due to its side effect profile, the NSRI venlafaxine should be reserved for use in the treatment of refractory depression. *See* Ruoff page S30.

Furthermore, Ruoff discloses that a selective serotonin reuptake inhibitor (SSRI), such as fluoxetine, sertraline and paroxetine, are considered the *first-line treatment* for depression because of the demonstrated efficacy and well tolerated side-effect profile (*see* Ruoff page S28) and that tricyclic antidepressants are considered *second or third-line therapy* when compared to the newer antidepressants (e.g., SSRIs) due to the fact that SSRIs are better tolerated.

Thus, Ruoff not only fails to teach the desirability of the claimed method, but in fact teaches away from using an NSRI or TRI, as claimed in the present invention. The only NSRI disclosed in Ruoff (venlafaxine) is taught to be associated with serious side-effects.

Consequently, there is simply no motivation to combine Ruoff with the other cited references, and one of ordinary skill in the art would have no reasonable expectation, based on the teachings of Ruoff, that a dual norepinephrine serotonin reuptake inhibitor (NSRI) or triple reuptake inhibitor (TRI) could successfully be used to treat at least one symptom of atypical depression secondary to pain, as recited in the present claims.

Thus, reconsideration and withdrawal of the rejection of claims 1-7 and 12-13, as obvious over Mouzin in view of Moret and Ruoff, is respectfully requested.

Claim 8 stands rejected under 35 U.S.C. § 103(a) as obvious over Mouzin in view of Moret and Ruoff, further in view of Shuto *et al, J. Med. Chem.*, 38 2964-68 (1995) ("Shuto").

While Applicants respectfully disagree with the Examiner, in order to further prosecution of this application, claim 8 has been canceled, rendering this rejection moot.

Claim 9 stands rejected under 35 U.S.C. § 103(a) as obvious over Mouzin in view of Moret and Ruoff, further in view of Puech *et al.*, *Inter. Clinical Psychopharmacology*, 12, 99-108 (1997) ("Puech").

While Applicants respectfully disagree with the Examiner, in order to further prosecution of this application, claim 9 has been canceled, rendering this rejection moot.

VI Conclusion

No new matter has been added by these amendments. In view of the arguments and amendments set forth above, each of the presently pending claims in this application is believed to be in immediate condition for allowance.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

By _____

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